Armed Forces College of Medicine

AFCM

1- Gluconeogenesis

BY

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INTENDED LEARNING OBJECTIVES (ILOs)

By the end of this lecture the student will be able to:

1. Discuss Biochemical importance of gluconeogenesis
2. Mention different gluconeogenic substrates
3. Illustrate different gluconeogenesis pathways

Outlines

- What is gluconeogenesis
- Gluconeogenic substrates
- Gluconeogenesis pathways
- Biochemical importance of gluconeogenesi

What is gluconeogenesis

Brain fuels

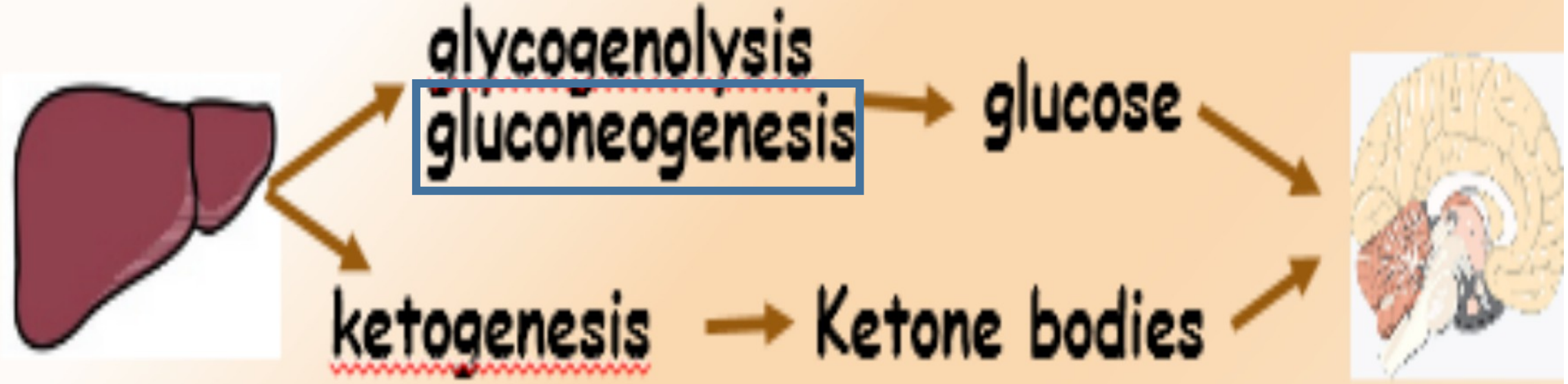
- **They are food stuffs that supply the brain with energy.**

- **The brain is an energy-hungry organ as it uses ten times more energy than the rest of the organs.**

What are the different sources of brain fuels during well-fed state?

Dietary carbohydrates are digested giving **glucose** which is the main fuel of the brain.

What are the different sources of brain fuels during fasting state?



Case presentation

A patient 45 years old with a history of liver cell failure developed hypoglycemia during prolonged fasting

WHY?

After an overnight fast, 75-80% of glucose released into the circulation derives from the liver and the remaining 20-25% derives from the kidneys

Gluconeogenesis

All pathways responsible for formation of glucose from non carbohydrate sources.

Examples: **lactate ,aminoacids, glycerol & propionyl COA**

Organs involved in gluconeogenesis

- In liver (major site) & kidney cortex. These organs contain complete set of enzymes required for synthesis of glucose from non carbohydrate sources

- Occurs partially in mitochondria and partially in the cytosol

Gluconeogenic substrates

Substrates of

Lactate

Glycerol

Amino acids

Propionyl COA

Gluconeogenesis pathways

1- Gluconeogenesis from lactate

Sources of Lactate:

From anaerobic tissues as:

RBCs,

Renal medulla,

Retina,

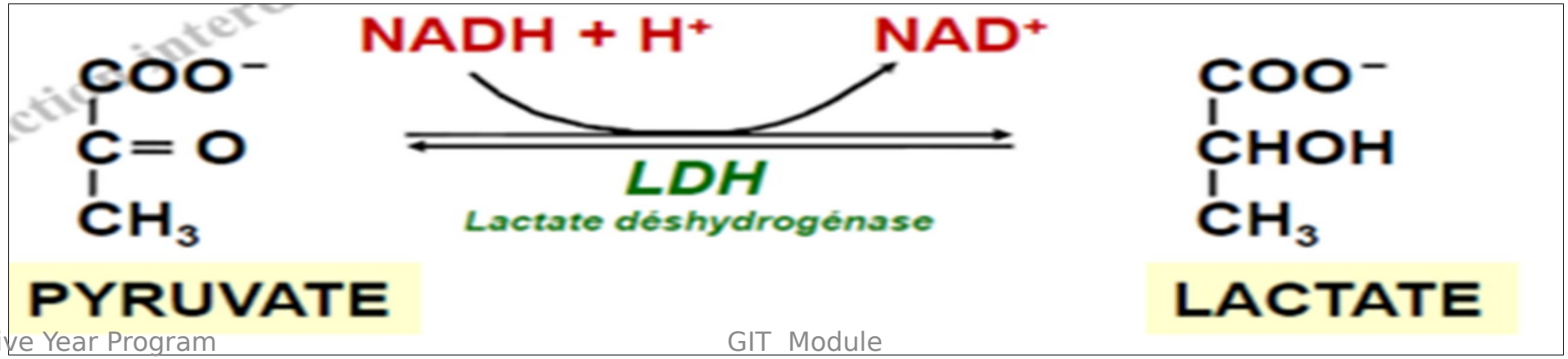
Lens,

Testis, and

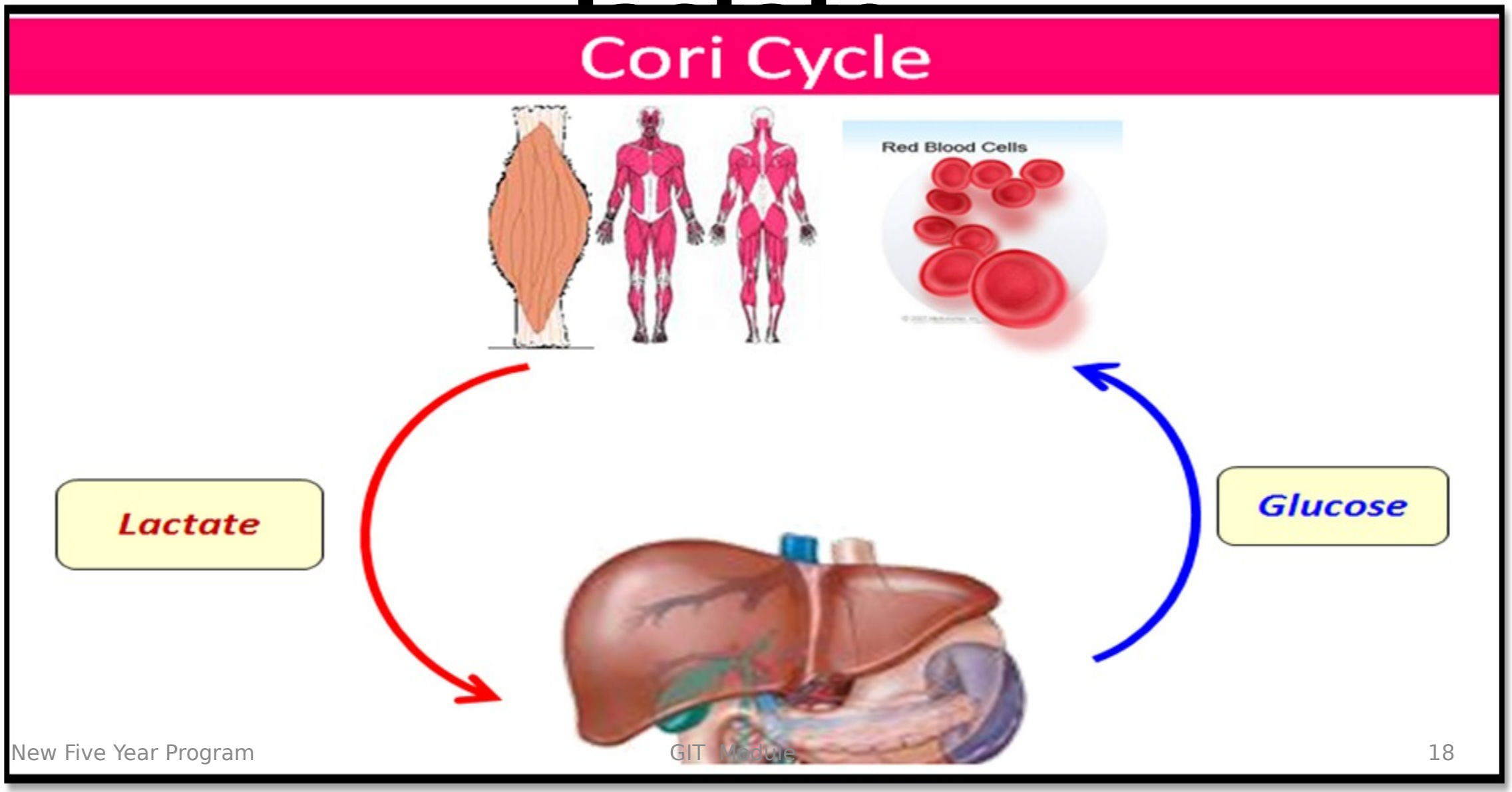
From sever muscular exercise

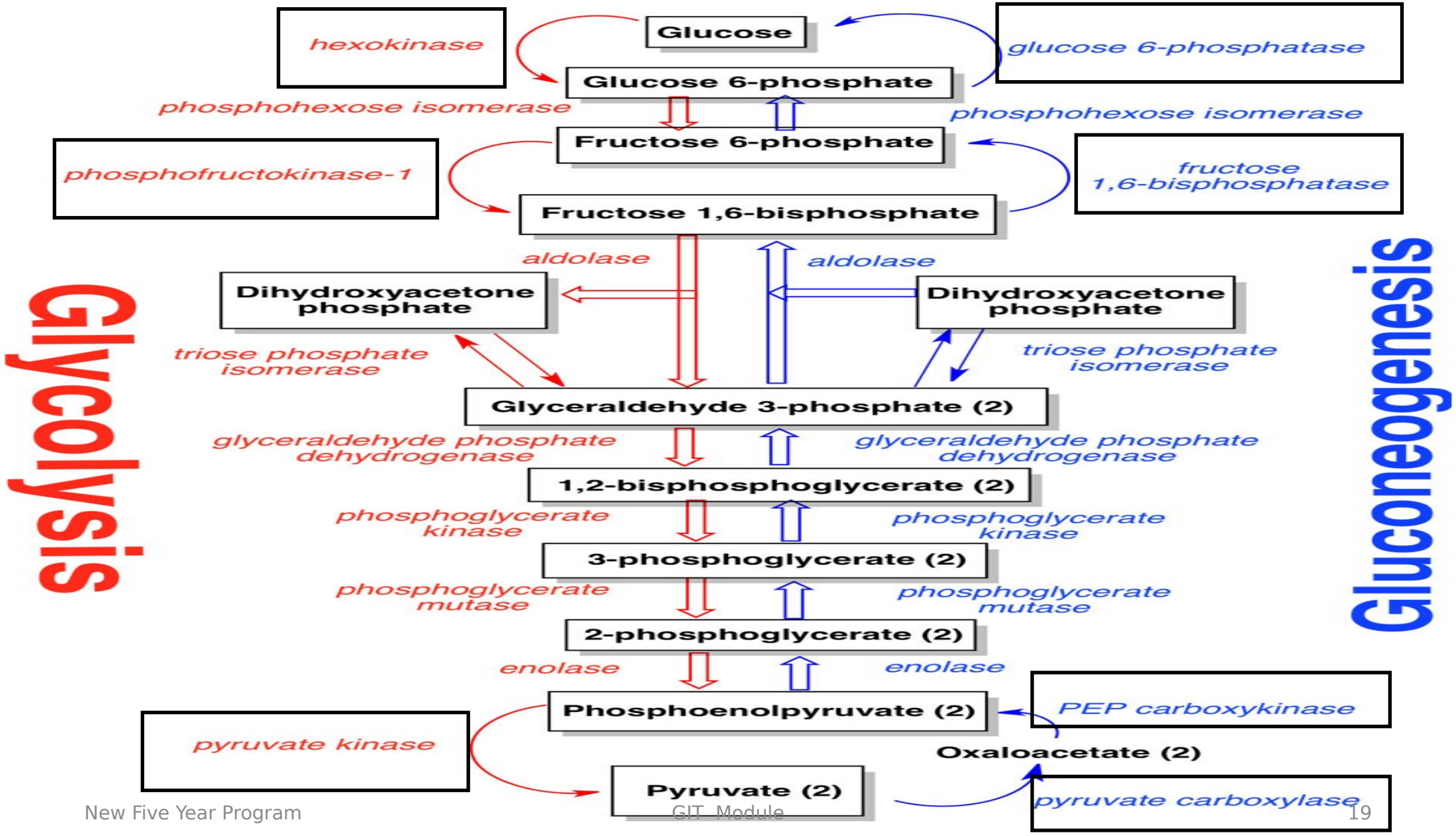
1- Gluconeogenesis from lactate

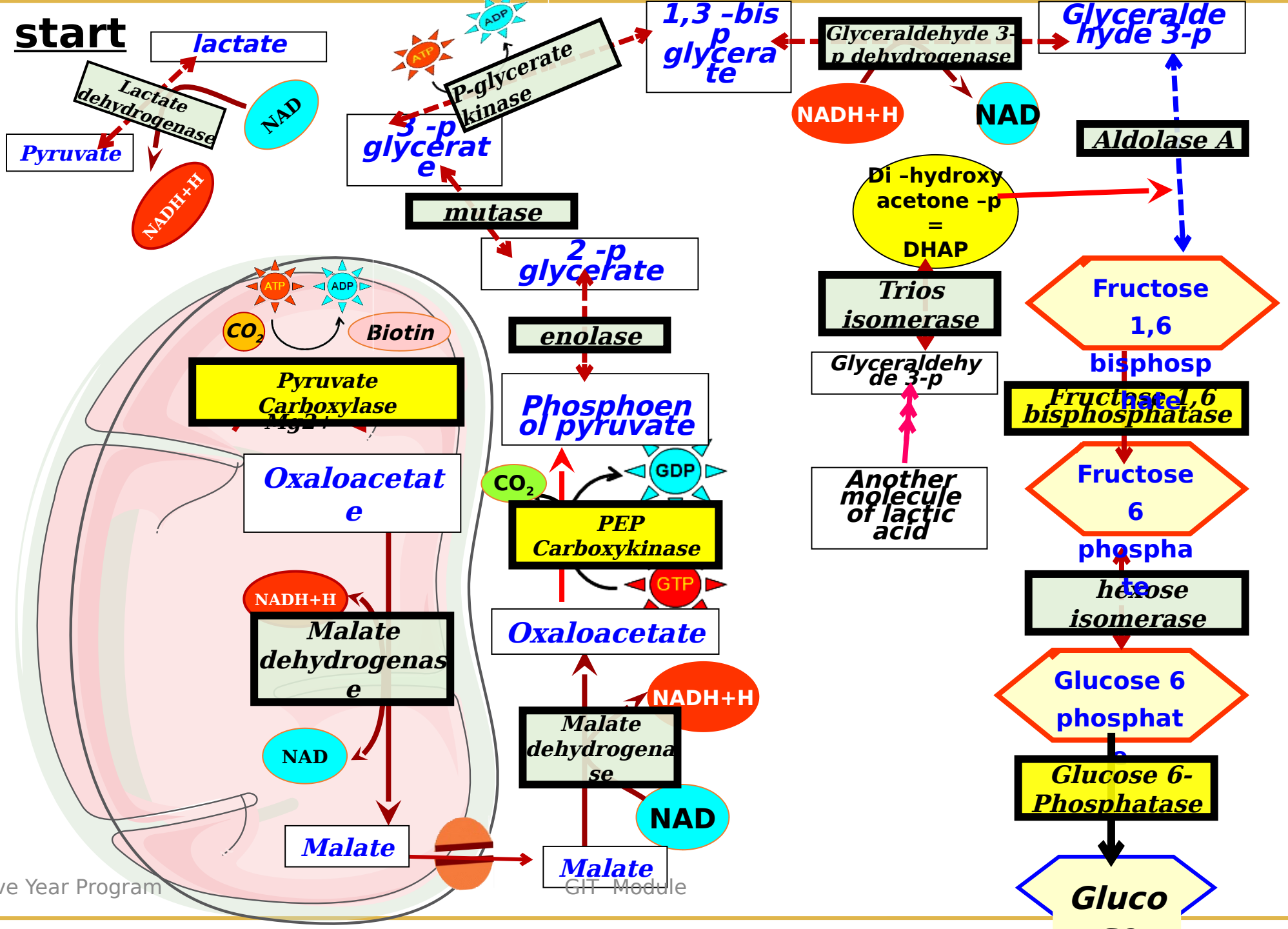
Lactate is released & delivered to the liver and reconverted to pyruvate by lactate dehydrogenase then →→ glucose (by gluconeogenesis), which is released back into the



1- Gluconeogenesis from lactate




Glycolysis
Gluconeogenesis
hexokinase
Glucose
glucose 6-phosphatase
Glucose 6-phosphate
phosphohexose isomerase
phosphohexose isomerase
Fructose 6-phosphate
phosphofructokinase-1
fructose 1,6-bisphosphatase
Fructose 1,6-bisphosphate
aldolase
aldolase
Dihydroxyacetone phosphate
Dihydroxyacetone phosphate
triose phosphate isomerase
triose phosphate isomerase
Glyceraldehyde 3-phosphate (2)
glyceraldehyde phosphate dehydrogenase
glyceraldehyde phosphate dehydrogenase
1,2-bisphosphoglycerate (2)
phosphoglycerate kinase
phosphoglycerate kinase
3-phosphoglycerate (2)
phosphoglycerate mutase
phosphoglycerate mutase
2-phosphoglycerate (2)
enolase
enolase
Phosphoenolpyruvate (2)
PEP carboxykinase
Oxaloacetate (2)
pyruvate kinase
Pyruvate (2)
pyruvate carboxylase


start
lactate
Lactate dehydrogenase
NAD
Pyruvate
NADH+H
ATP
ADP
P-glycerate kinase
1,3 –bis p glycera te
3 -p glycerat e
mutase
2 -p glycerate
enolase
Phosphoen ol pyruvate
CO2
Biotin
Pyruvate Carboxylase
Mg2+
Oxaloacetat e
PEP Carboxykinase
GDP
GTP
Oxaloacetate
NADH+H
Malate dehydrogenas e
NAD
Malate
Malate dehydrogena se
Glyceraldehyde 3-p dehydrogenase
Glyceralde hyde 3-p
Aldolase A
Di –hydroxy acetone –p = DHAP
Trios isomerase
Glyceraldehy de 3-p
Another molecule of lactic acid
Fructose 1,6 bisphosp hate
Fructose 1,6 bisphosphatase
Fructose 6 phospha te
hexose isomerase
Glucose 6 phosphat
Glucose 6-Phosphatase
Gluco

Note:

- we need 2 lactate molecules to produce one glucose molecule

- Pyruvate carboxylase enzyme is a mitochondrial enzyme

- PEPCK reaction is driven by hydrolysis of GTP.

The 3 irreversible enzymes of glycolysis are reversed as follow:

- **Pyruvate Kinase: by Pyruvate Carboxylase & phosphoenol pyruvate carboxykinase (PEPCK).**

- **PhoshoFructoKinase I: by Fructose 1,6 bisphosphatase.**

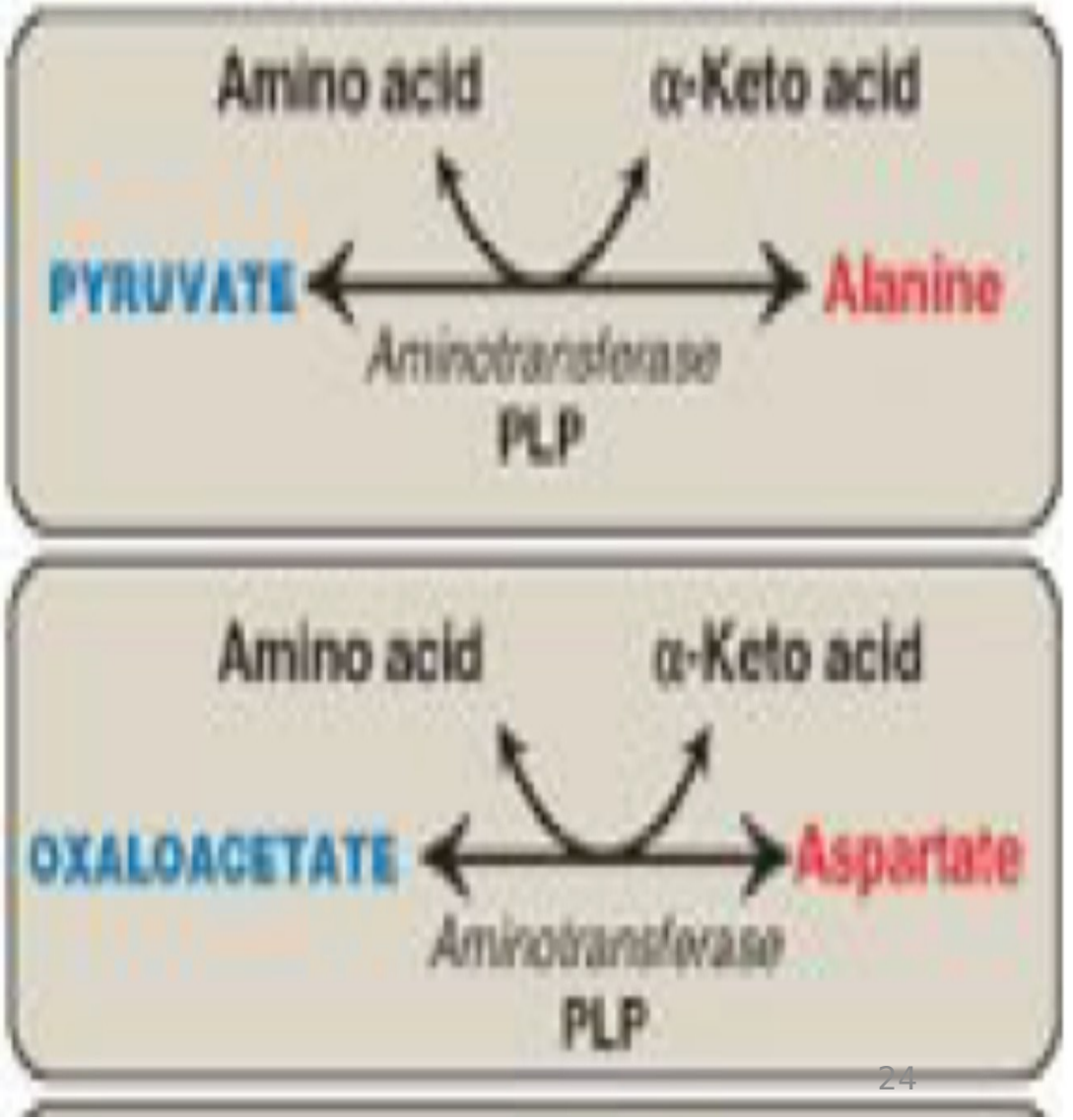
- **Hexokinase/glucokinase: by Glucose 6 phosphatase.**

2- Gluconeogenesis from Amino acids

- **Aminoacids (mostly Alanine & glutamine) from muscle proteolysis are the major source of glucose during prolonged fasting & starvation.**

2- Gluconeogenesis from Amino acid

- **Amino acids are metabolized 1st to release NH3 through deamination or transamination to give pyruvic or oxalacetate**



2- Gluconeogenesis from Amino acids

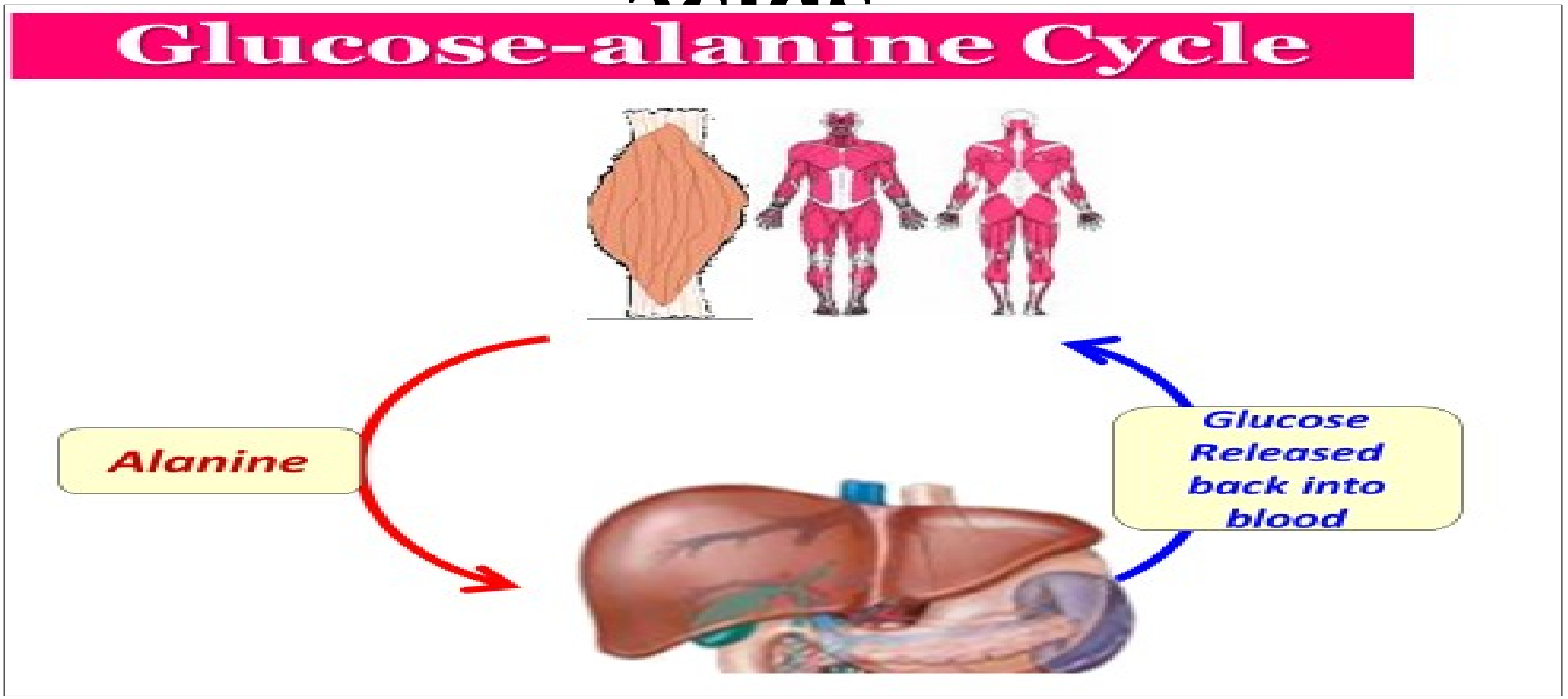
Alanine is one of the predominant aminoacid released during prolonged fasting from muscle & delivered to the liver

and reconverted to glucose by Alanine transaminase , which is

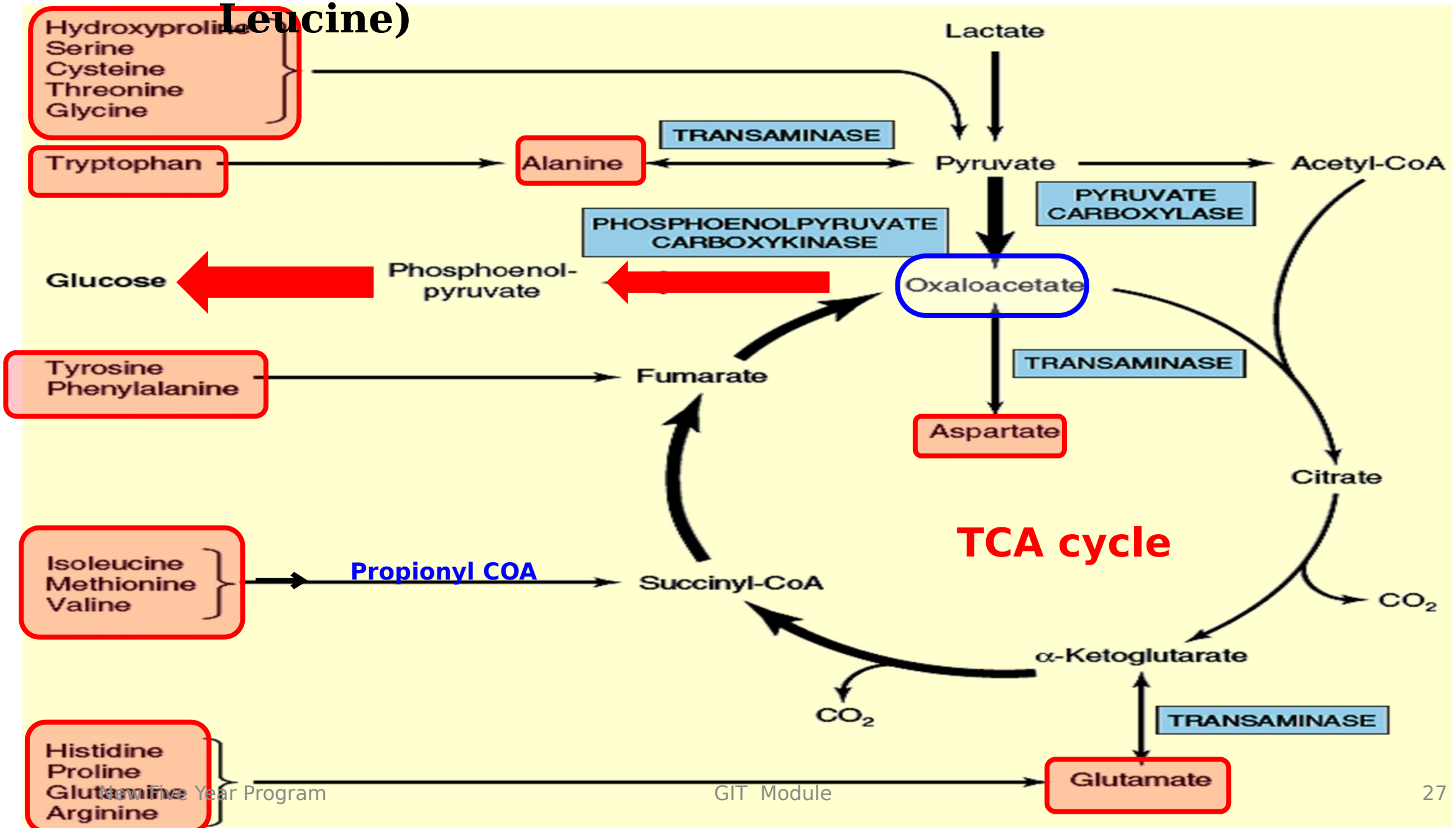
released back into the circulation

(Glucose-alanine Cycle).

2- Gluconeogenesis from Amino acids

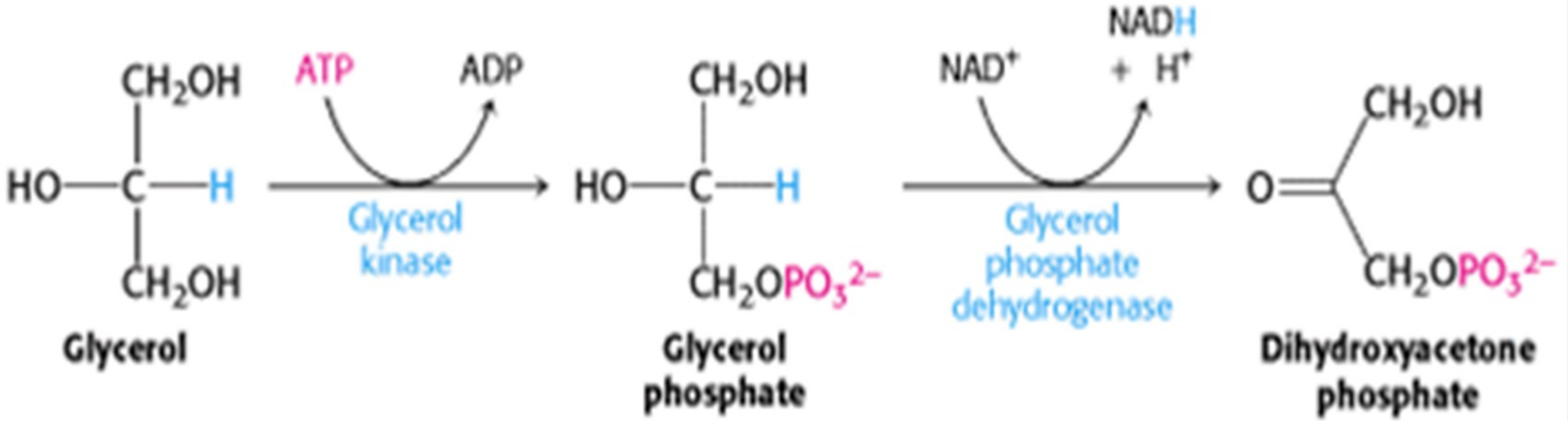


All A.As can give →→ Glucose Except (Lysine & Leucine)



3- Gluconeogenesis from Glycerol

- **Glycerol is released during Lipolysis & delivered to the liver.**



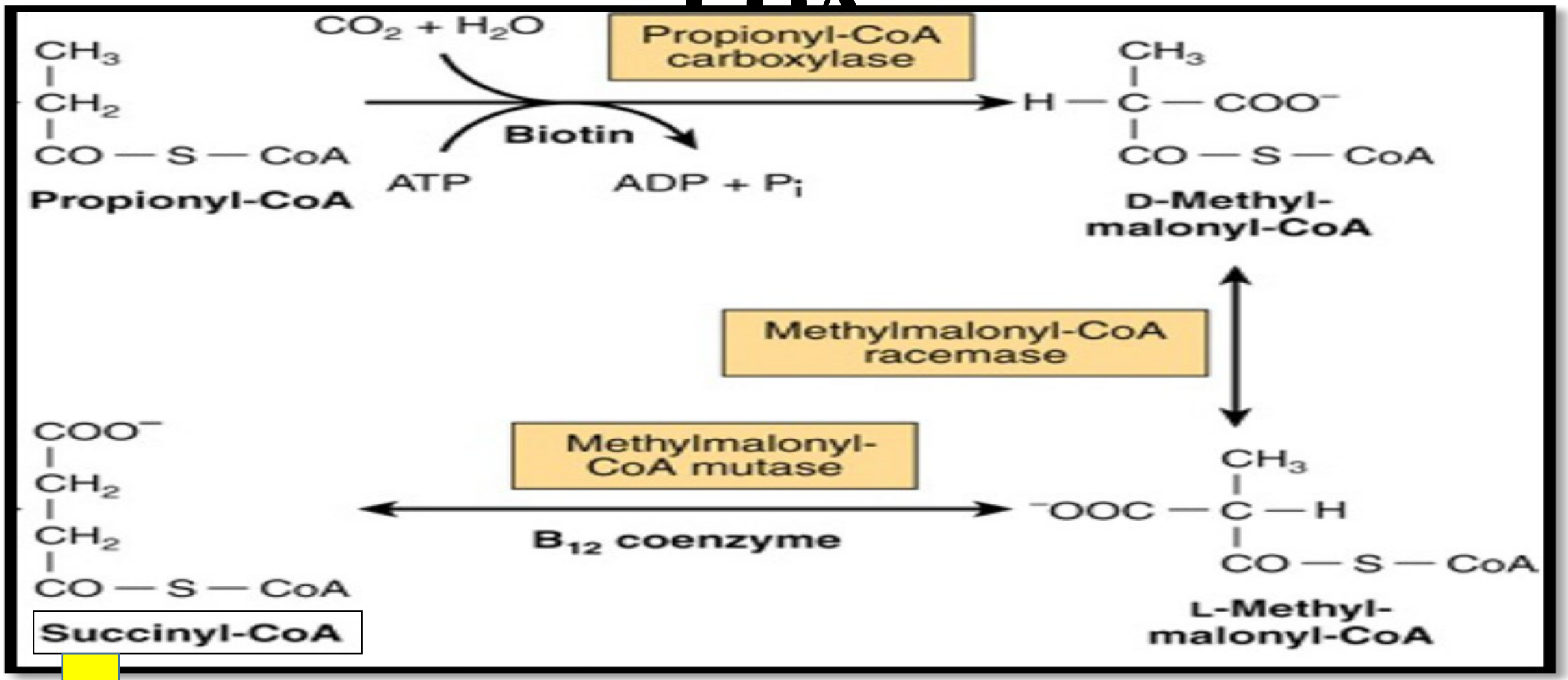
4- Gluconeogenesis from Propionyl COA

It is a product of oxidation of odd-number fatty acids & catabolism of amino acids as valine , isoleucine & methionine.

N.B.

It is not a significant glucogenic precursor in human beings

4- Gluconeogenesis from Propionyl COA



Glucose

Lecture Quiz

Which one of the following reactions is unique to gluconeogenesis?

A. Lactate → pyruvate
B. Phosphoenolpyruvate → pyruvate
C. Oxaloacetate → phosphoenolpyruvate
D. Glucose 6-phosphate → fructose 6 phosphate
E. 1,3-Bis-phosphoglycerate → 3-phosphoglycerate

Energy requirement in gluconeogenesis to form 1 glucose molecule is dependant on starting point:

- Starting with 2 pyruvate cost 6 ATP:2 × (1 ATP for pyruvate carboxylase + 1 ATP for phosphoglycerate kinase + 1 GTP for PEPCK)
  - Starting with 2 oxaloacetate cost 4 ATP
  - Starting with 2 glycerol we need 2 ATP

Gluconeogenesis is a costly metabolic process

Biochemical importance of gluconeogenesis

Biochemical importance of gluconeogenesis

1.Maintain a basal level of glucose in the circulation during prolonged fasting & starvation this is because…

- ***Brain has a minimum requirement of 120g glucose/day***
- ***Glucose is the main source of energy to anaerobic cells ex: RBCs***

2. Gluconeogenesis also help To clear lactate and prevent lactic acidosis.

So, gluconeogenesis is active in the following conditions:

1- During prolonged fasting & starvation: it begins nearly 6 hrs after last meal & become fully active after complete depletion of liver glycogen (10-18 hrs).

2- Unbalanced diet (decrease carbohydrates & increase fat and/or protein).

So, gluconeogenesis is active in the following conditions:

3- Type I diabetes mellitus (stimulation of enzymes of gluconeogenesis).

4- Cushing syndrome (high cortisol level stimulate muscle proteolysis & enzymes of gluconeogenesis).

5- Sever muscle exercise (increase lactate which is a substrate of gluconeogenesis).

Take Home Message

- **Gluconeogenesis:**
  Synthesis of glucose from noncarbohydrates
  Anabolic & Energy-consuming

- **Four unique enzymes are required for the reversal of the 3 irreversible reactions of glycolysis**

- **Both gluconeogenesis & glycolysis are reciprocally-regulated**

- **Impaired gluconeogenesis leads to fasting hypoglycemia and may cause lactic acidosis**

Thank you

Marwa Ali